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Scientific Article

Pentoxifylline and vitamin E drug compliance after adjuvant breast radiation therapy

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Abstract

Purpose: Breast fibrosis is a common late effect after therapeutic irradiation that can result in pain, poor cosmesis, and functional impairment. Randomized trials have demonstrated that radiation fibrosis may be preventable with a medication regimen of pentoxifylline and vitamin E. This study investigates patient compliance with pentoxifylline therapy while examining possible correlations to compliance.

Methods and materials: We identified 90 patients who were prescribed pentoxifylline (400 mg 3 times daily) and vitamin E (400 IU once daily) after adjuvant breast radiation. A retrospective cohort study was conducted using medical record analysis. Data were collected, including patient age, comorbid conditions, concurrent medications, duration of pentoxifylline and vitamin E therapy, dose adjustments, patient-reported side effects, and cause for discontinuation. A multivariate analysis of the correlation between medication compliance and these categorical variables was assessed with a χ^2 analysis of independence.

Results: Patient compliance with pentoxifylline and vitamin E therapy was found to be poor in 33 of 87 patients (38%) in the cohort, necessitating either dose reductions or discontinuation of therapy. There was a statistically significant correlation between concurrent antiemetic therapy and successful completion of pentoxifylline regimen. Of those on antiemetic therapy, 89% completed pentoxifylline as prescribed versus 48% of those without antiemetics ($P < .001$). There was a statistically significant correlation between concurrent proton pump inhibitor (PPI) therapy and discontinuation of pentoxifylline. Of those on PPI therapy, 33% completed pentoxifylline versus 81% of those not on PPIs ($P < .001$). All other variables examined were not significantly correlated with compliance.

Conclusions: Patient compliance with pentoxifylline appears to be worse in clinical practice compared with previously published studies. Nausea was the most frequently reported indication for treatment modification or discontinuation. Concurrent antiemetic therapy was correlated with strong regimen compliance, but concurrent PPI therapy was correlated with poor compliance, independent of comorbid conditions.

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Introduction

Radiation therapy is an important component in the curative management of early stage breast cancer. With ever-improving rates of survival for patients with breast cancer, late effects of cancer treatment have become increasingly relevant. Radiation fibrosis is a common late effect after therapeutic irradiation that can result in pain, poor cosmesis, and functional impairment of the irradiated breast, chest wall, or shoulder. Data from multiple clinical trials suggest that a medication regimen of pentoxifylline combined with vitamin E may prevent or reverse radiation-induced breast fibrosis.[1-3] A pivotal phase 3, placebo-controlled, randomized clinical trial found a significant improvement in breast tissue compliance in patients who received treatment with pentoxifylline and vitamin E versus placebo after undergoing breast radiation.[3] Physicians have subsequently increased the use of this regimen to decrease the incidence and severity of radiation fibrosis.

Pentoxifylline is a methylxanthine derivative that was originally developed as a therapeutic agent in the treatment of circulatory issues such as peripheral vascular disease.[4] Although the precise mechanism remains in dispute, pentoxifylline is thought to increase red and white cell membrane plasticity, which subsequently decreases blood viscosity, platelet aggregation, and fibrinogen levels.[5] Thus, it was suggested that pentoxifylline may alter human dermal fibroblast proliferation and extracellular matrix production and increase collagenase activity. This mechanism of action prompted investigations of pentoxifylline as a potential agent in the management or prevention of radiation-induced fibrosis.[6] The pathogenesis of radiation-induced fibrosis is thought to be secondary to free radical generation and subsequent damage to microvascular endothelial cells.[7] This damage initiates an inflammatory response that is mediated by the release of numerous proinflammatory cytokines.[8]

The most well studied cytokine in this pathway is transforming growth factor β1 (TGFβ1), which stimulates the activation of fibroblasts into collagen-synthesizing myofibroblasts. These activated myofibroblasts independently synthesize TGFβ1 and create a positive feedback loop.[9] Autocrine signaling subsequently induces the continued deposition of collagen in the extracellular matrix independent of continued inflammatory stimuli. It has been proposed that pentoxifylline breaks this cycle by inhibiting the TGF β1 feedback cascade, thus allowing for unopposed fibrinolysis by metalloproteinase, which lyses collagen and allows for fibrosis reversal.[10]

Clinical trials evaluating pentoxifylline for breast fibrosis have consistently reported an excellent safety and tolerability profile. Jacobson et al reported a 96% compliance rate with pentoxifylline therapy. Only 1 of 26 patients on the treatment arm discontinued therapy, and this was because of the development of a rash.[3] Another trial reported 94% compliance with the treatment regimen. Only 5 of 68 patients discontinued therapy, and none of the discontinuations were due to medication side effects.[2] In yet another trial, none of the patients discontinued therapy or experienced side effects.[1] These clinical trials had excellent follow-up and patient compliance with pentoxifylline therapy, and 1 trial even used weekly nursing checks to evaluate and ensure prescription refills.[3] Although it has been established that pentoxifylline and vitamin E therapy compliance is good in the setting of a clinical trial, it remains unclear how tolerable the regimen is in clinical practice.

The pentoxifylline tolerance and compliance data reported in the radiation oncology literature are excellent. In contrast, numerous studies conducted in other disease sites have found significantly higher rates of gastrointestinal (GI) side effects. A meta-analysis of clinical trials that evaluated pentoxifylline efficacy and tolerability in patients with peripheral vascular disease found that the majority of reported side effects were GI disturbances, with >30% of patients discontinuing the medication due to side effects.[11] The incidence of reported side effects varied greatly among studies, with some series reporting zero adverse events and others reporting a > 50% incidence of adverse events.[12] Although compliance with pentoxifylline is high in studies of radiation-induced breast fibrosis, it remains unclear how tolerable the regimen is in clinical practice.

At our institution, we have been using pentoxifylline and vitamin E in patients deemed at risk for developing fibrosis after adjuvant breast radiation therapy. We conducted a retrospective study to examine a cohort of patients with breast cancer who received pentoxifylline and vitamin E therapy for the prevention or treatment of radiation-induced fibrosis. We sought to identify overall pentoxifylline regimen compliance in the clinical setting while evaluating patient characteristics, diagnoses, and concurrent medications, which are correlated with compliance outcomes.

Methods and materials

Ethical approval for this retrospective cohort study was obtained from the institutional review board. Medical records were retrospectively identified using an institutional bioinformatics electronic warehouse, which is capable of scanning and extracting key pieces of data from electronic medical records. Patients treated at our institution from January 2013 to December 2015 were included in this review. Additional screening criteria included the following: female sex, invasive breast cancer or ductal carcinoma in situ, history of breast or chest wall radiation therapy, prescription for pentoxifylline 400 mg 3 times daily, and at least 6 months of postradiation follow-up. Data were then collected, including patient age, comorbid conditions, concurrent medications, concurrent chemotherapy, duration of pentoxifylline and vitamin E therapy, dose adjustments to

the regimen, patient-reported side effects, and any reported reason for discontinuation.

Patients were defined as compliant with treatment if they remained on the medication at any dose after receipt of the prescription. Patient age was defined as age at the initiation of pentoxifylline therapy. Comorbid conditions were defined as conditions on a patient's problem list at initiation of pentoxifylline therapy. Concurrent medications, including chemotherapy, were identified as any medications on a patient's medication list at initiation of pentoxifylline therapy and any medications that were initiated during the regimen. Duration of therapy was defined as the time from initiation of pentoxifylline to the time of documented discontinuation for any reason.

At our institution, pentoxifylline therapy is prescribed for a duration of 6 months. At completion of the 6-month duration of therapy, patients are given the option to receive another 6 months of treatment at their own discretion. Because of the variability in patient continuation after the standard 6-month prescription, the cohort was only evaluated during the standard 6-month prescription. Patients who were prescribed pentoxifylline for less than 6 months were excluded. Medication lists were updated at every patient visit, regardless of the provider. Drug discontinuation dates were recorded at each encounter as medication lists were updated to ensure an accurate historical timeline of medication adherence.

Statistical analyses were performed on the data set. Standard descriptive statistics such as frequencies, mean, and median were computed for each variable. Univariate analysis of correlation between medication compliance and the aforementioned list of categorical variables was assessed with a χ^2 analysis of independence in addition to relative risk using SAS-JMP, Version 12 (SAS Institute Inc., Cary, NC). In cases in which an expected outcome was less than 5, a 2-tail Fisher's exact test was performed to analyze independence. Multivariate analysis of correlation was performed with a binominal logistic fit regression model. A *P*-value of <.05 was considered statistically significant.

Results

The electronic medical record query identified 90 patients who met the established inclusion criteria. From that cohort, 3 patients were excluded due to loss of follow-up (n = 1) and incomplete chart data (n = 2). The final number of patients examined in this cohort was 87. Patient demographics and distribution of patient variables are outlined in Table 1. A total of 25 patients (28.7% of the cohort) discontinued pentoxifylline prior to completion of the planned therapy. Thirty-three patients (37.9%) reported symptoms of any kind. The most commonly reported symptoms were GI-related, with 26 patients reporting nausea, 6 patients reporting abdominal pain, and 1 patient reporting diarrhea. A total of 13 patients required a dose reduction of pentoxifylline, with 5 eventually discontinuing completely due to side effects. Among patients who discontinued therapy, the median time to discontinuation was 2 months. Patient attrition continued throughout the duration of the planned therapy (Fig 1).

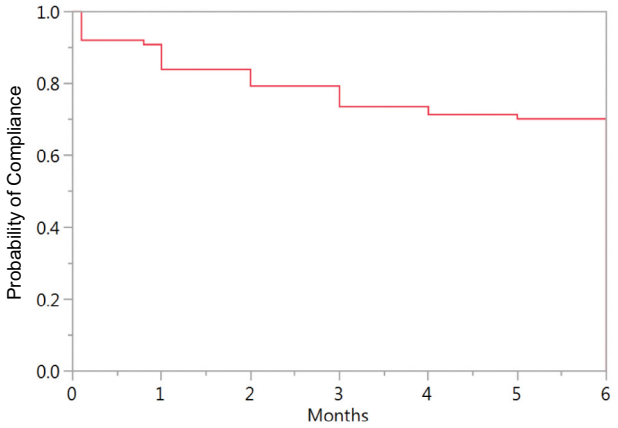

Figure 1 This Kaplan-Meier curve depicts the probability of patient compliance with pentoxifylline therapy over the prescribed 6 months. At the end of the 6 month course of the medication regimen, 28.7% of patients discontinued pentoxifylline due to intolerable symptoms.

On univariate analysis, several variables were associated with pentoxifylline regimen compliance. Patient ethnicity was initially found to be correlated with symptom-related regimen discontinuation. Approximately 19% of Caucasian patients discontinued therapy, whereas 35% of African-American and 50% of Hispanic/Latino patients discontinued therapy due to symptoms ($P = .0364$). Patients who were prescribed ondansetron during pentoxifylline therapy were statistically more likely to complete the full course. A statistically significant correlation was found between concurrent antiemetic therapy and successful completion of the prescribed pentoxifylline regimen. Of those patients on antiemetic therapy, 89% completed pentoxifylline as prescribed. Of the patients not taking antiemetics, only 48% of patients were able to complete pentoxifylline therapy ($P < .001$).

The other notable variable that was associated with compliance was concurrent proton pump inhibitor (PPI) use. There was a statistically significant correlation between concurrent PPI therapy and discontinuation of pentoxifylline. Of those patients on concurrent PPI therapy, only 33% completed pentoxifylline as prescribed. Of the patients not on PPIs, 81% were able to complete therapy as prescribed ($P = .008$). Notably, a diagnosis of gastroesophageal reflux disease was not significantly associated with pentoxifylline compliance. All other comorbidities, medications, and age were not associated with medication compliance.

The results of the final multivariate analysis are shown in Table 1. Upon evaluation of all gathered variables, only concurrent ondansetron ($P < .001$) and concurrent PPI

Table 1 Outcomes of examined variables with associated univariate and multivariate analyses

Variable	Total Number	Symptom-Induced Discontinuation (% of Cohort)	Completion of Regimen (% of Cohort)	Univariate *P*-value	Multivariate *P*-value
Overall Compliance	87	25 (28.7)	62 (71.2)		
Age, y					
<40	7	2	5	.1108	.1803
≥40 and <50	20	6	14		
≥50 and <60	25	9	16		
≥60 and <70	21	7	14		
≥70	14	1	13		
Race					
White	52 (59.8)	10 (11.5)	42 (48.3)	.0364[a]	.0869
African American	17 (19.5)	6 (6.9)	11 (12.6)		
Hispanic	18 (20.7)	9 (10.3)	9 (10.3)		
Reported Symptoms	33 (37.9)	25	8		
Nausea	26	20	6		
Diarrhea	1	1	0		
Abdominal Pain	6	4	2		
Dose Reduction					
Yes	13	5	8		
No	74				
Comorbidities					
Diabetes	11 (12.6)	4 (4.6)	7 (8.1)	.7223[b]	.6948
GERD	16 (18.4)	3 (3.45)	13 (14.9)	.5413[b]	.6777
Irritable Bowel Syndrome/Inflammatory Bowel Disease	7 (8.1)	1 (1.2)	6 (6.9)	.6678[b]	.7822
Psychiatric Disorder	20 (23.0)	9 (10.3)	11 (12.6)	.0670	.6900
Migraine	10 (11.5)	4 (4.6)	6 (6.9)	.4637[b]	.2040
Medications					
Vitamin E	74	23 (26.4)	51 (58.6)	.2487	.0665
Aromatase Inhibitor	40	11 (12.6)	29 (33.3)	.814	.2664
Tamoxifen	31	10 (11.5)	21 (24.1)	.589	.3936
Proton Pump Inhibitor	18	12 (13.8)	6 (6.90)	.0080[a,b]	.0007[a]
Ondansetron	45	5 (5.75)	40 (46.0)	.0003[a,b]	.0002[a]
Chemotherapy	10	5 (5.75)	5 (5.75)	.146[b]	.0667

[a] Statistically significant.
[b] Fisher's exact test statistic.

therapies ($P \leq .001$) were statistically significant. Patient ethnicity did not hold up as statistically significant on multivariate analysis ($P = .0869$). These results remained stable with both forward and backward selection procedures in the multivariate model.

Discussion

The aim of this study was to investigate patient compliance with pentoxifylline therapy in patients being treated for radiation fibrosis of the breast and to determine possible correlates to compliance. We found high rates of drug discontinuation, primarily attributed to GI side effects. The results of this retrospective cohort study display a statistically significant correlation between pentoxifylline regimen compliance and concurrent medication with ondansetron or PPI. Patients on ondansetron were significantly more likely to complete the planned course of pentoxifylline therapy. Conversely, patients taking concurrent PPI therapy completed pentoxifylline therapy at a significantly lower rate than those not on PPI therapy.

As previously mentioned, clinical trials evaluating the efficacy of pentoxifylline for radiation fibrosis showed excellent patient compliance with the regimen. Our data suggest that in clinical practice, up to one-third of patients on pentoxifylline therapy are unable to complete the prescribed regimen due to side effects. The overall rate of pentoxifylline therapy discontinuation in this cohort was 28.7%, which is congruent with published studies of pentoxifylline use for other indications.[11] In 1 trial evaluating pentoxifylline in patients with lower extremity claudication, up to 55% of patients reported intolerable side effects, primarily of GI etiology and with nausea being most

pronounced.[12] A meta-analysis of pentoxifylline efficacy and tolerability found that more than 30% of patients cited medication side effects as the reason for withdrawal from the trials.[11] These results seem to support the findings in this study.

Two randomized clinical trials have demonstrated the efficacy of pentoxifylline in combination with vitamin E in the treatment and prevention of radiation-induced fibrosis of the breast. Delanian et al performed a double-blind, placebo-controlled study in women who had previously received radiation therapy for breast cancer. This trial found a significant reduction in the volume of fibrotic tissue at 6 months in patients who were treated with pentoxifylline and vitamin E.[1] Based on these findings, Jacobson et al conducted a phase 3 clinical trial randomizing women who were treated with whole breast irradiation to pentoxifylline and vitamin E versus placebo. A tissue compliance meter was used to objectively measure changes in breast tissue compliance relative to the untreated breast. At the end of 6 months, breast tissue compliance was better in patients who were treated with pentoxifylline and vitamin E compared with the placebo. The clinical efficacy of pentoxifylline therapy has been established clearly in these trials; however, the reported tolerability of the regimen continues to be variable in the published literature.

Jacobson et al reported a 96% compliance rate with pentoxifylline therapy. Only 1 of 26 patients in the treatment arm discontinued therapy, and this was because of the development of a rash.[3] In the trial by Delanian et al, no patients discontinued pentoxifylline therapy as a result of side effects. Another trial reported 94% compliance with the treatment regimen. Only 5 of 68 patients discontinued therapy, and none of the discontinuations were due to medication side effects.[2] These clinical trials had excellent follow-up and patient compliance with pentoxifylline therapy and included weekly nursing checks to evaluate and ensure prescription refills.[3]

Our data show that patients taking ondansetron were significantly more likely to complete the prescribed course of pentoxifylline. Ondansetron is a potent and highly selective antagonist of the serotonin receptor 5-HT3 indicated for the treatment of moderate-to-severe nausea and vomiting. Ondansetron is frequently used for chemotherapy-induced nausea and vomiting. Patients in our data set may or may not have been actively taking ondansetron concurrently with pentoxifylline therapy, but it is possible that patients with existing prescriptions for ondansetron were medicating themselves to mitigate the GI-related side effects of the regimen.

Our data show that patients taking a PPI were significantly more likely to prematurely discontinue the prescribed course of pentoxifylline. Interestingly, a diagnosis of gastroesophageal reflux disease, for which PPIs are commonly prescribed, did not correlate with pentoxifylline discontinuation on univariate or multivariate analyses. One possible explanation for this could be that patients commonly take over-the-counter PPI for mild or intermittent reflux symptoms without an official diagnosis of gastroesophageal reflux disease. It is also possible that the 2 events are truly not related, and PPI inhibitor is indeed a true correlate to pentoxifylline discontinuation.

One plausible hypothesis to explain this relationship lies in the pharmacokinetics of the 2 molecules. Omeprazole, a common PPI reported in our data set, has been shown to be a strong inducer of cytochrome P450 (CYP) 1A2.[13] In an in vivo analysis, pentoxifylline has been shown to undergo metabolism by CYP 1A2.[14] Interestingly, in this study, ciprofloxacin's effects on CYP 1A2 was shown to result in a 2-fold increase in serum concentration of pentoxifylline and its first metabolite M-1.[14] The increase in concentration of M-1 is significant because it is a methylxanthine with biologic activity similar to that of pentoxifylline. It has also been shown that an increase in plasma concentration of pentoxifylline and its active metabolites is positively correlated with a greater incidence of intolerable nausea symptoms.[15] It is conceivable that the inductive effects of omeprazole on CYP 1A2 could lead to higher serum concentrations of pentoxifylline's active metabolites, thus leading to the more pronounced GI side effects reported in this study. Further investigation of this mechanism and its implications on the data described herein is merited.

This study, as with any retrospective review, has inherent limitations. There are sources of uncertainty that lead to chance, bias, and confounding variables. Medical record errors, documentation errors, patient compliance reporting, side effect reporting, and other uncontrollable variables introduce their own uncertainties. One uncertainty included in our data is that patient prescription data were collected as a surrogate for concurrent medications, but there is no means of evaluating patient compliance at home. For example, it is possible that patients were prescribed a PPI but did not actually take the medication. It is also prudent to note that with this correlative data, correlation of variables does not imply causation. Yet, with the previously noted shortcomings, this study remains valuable as the initiating factor for future studies on the matter.

Conclusions

We found that pentoxifyline tolerance and compliance is significantly worse in a clinical practice setting than has been reported in randomized trials when used for prevention of radiation-induced breast fibrosis. A significant proportion of patients in our cohort experienced GI side effects that led to a dose reduction or discontinuation of the regimen. Ondansetron is associated with improved compliance, whereas PPI therapy is associated with worse compliance with pentoxifylline therapy. Going forward, this information should be used to better counsel patients prior

to the initiation of pentoxifylline therapy for the prevention of radiation-induced breast fibrosis.

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